On page 50, please amend the paragraph beginning at line 25 as follows:

• The CMV promoter (38-682) including the Kozak consensus translation initiation site was amplified by PCR with the PWO Polymerase® (Boehringer) with the following primer:

5' CCATGGCATAGCCCATATATGGAGTTCCGCG 3' (SEQ ID NO: 2)

5' TTGCTCACCATGGTGGCGA 3' (SEQ ID NO: 3)

IN THE SEQUENCE LISTING:

Please incorporate the Sequence Listing on the accompanying sheets, immediately following the "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**", into the present application.

REMARKS

Applicant has provided a paper copy of the Sequence Listing and the Sequence Listing in computer readable format. Subsequently, Applicant has amended the specification to conform to U.S. practices; specifically, the specification has been amended to incorporate a "SEQ ID NO:" for each sequence listed in the specification on pages 47 and 50. No new matter has been added.

I. Rejections to the claims under 35 U.S.C. § 102(e) and 103(a) over Maxwell et al.

The Examiner has rejected claims 3-7, 9-12, 14-16, 21 and 22 under 35 U.S.C. § 102(e) under Maxwell et al. (US Pat. No. 5,585,254) on the assertion that Maxwell et al. disclose autonomous Parvoviral gene delivery vehicles and expression vectors which are encompassed by the instant claims. In addition, the Examiner has rejected claims 8, 13, 21, and 28 under 35 U.S.C. § 103(a) over Maxwell et al. ('254) on the assertion that Maxwell et al. have taught autonomous Parvoviral gene delivery vehicles and expression vectors and that Maxwell et al. have described the correlative limitations in their parvoviral vectors.

Applicant respectfully submits herewith an English translation of the priority document, Belgian Application No. 09201087 (filed December 10, 1992), which has

been referenced in the Amendment responses previously filed on November 9, 1999 and September 17, 2001. As stated in these referenced Amendment responses, the Maxwell et al. patent ('254) does not constitute prior art to the instant claims which are directed to a nucleotide sequence comprising, *inter alia*, the nucleotide sequence of an oncoselective autonomous parvovirus for the destruction or normalization of cancer cells.

The present application is directed towards a "nucleic acid comprising the nucleotide sequence of an oncoselective autonomous parvovirus, and at least one effector nucleotide sequence encoding and effective polypeptide which effects the destruction or the normalization of cancer cells, wherein the effector nucleotide sequence comprises at least one sequence chosen from the group consisting of the nucleotide sequences that encode: a cytotoxic polypeptide or at least one fragment of this polypeptide, a molecule which confers on the transfected cell sensitivity to a radioactive toxic agent, at least one polypeptide or a fragment of this polypeptide which is capable of increasing an immune response, and at least one polypeptide or a fragment of this polypeptide which inhibits tumor neoangiogenesis," as recited in claim 10.

The accompanying English translation of the priority document substantiates the Applicant's claims that the instant application and accompanying priority document contain specific examples showing that it is possible to use the oncoselective characteristics of autonomous parvovirus to target cancer cells within a toxic agent. Applicant submits that several examples show it is possible to induce a cytotoxic polypeptide to a cell, a molecule that confers to the transfected cell sensitivity to a toxic agent, or a polypeptide that increases an immune response. Further, the parvoviral constructs encompassed in the instant claims can be produced in high amounts and retain oncoselectivity against cancer cells.

Applicant directs the Examiner's attention to page 9 of U.S. Application Serial No. 07/685,628, filed April 15, 1991, wherein viral vectors are generally described for the introduction of chimeric toxin genes into target cells. This application describes only retroviral vectors as the viral vectors, does not disclose or suggest alternative viral vectors, nor does it provide direction as to where one of skill in the art may turn for

further guidance. This aforementioned application serves as the parent application to Maxwell et al.'s Continuation-in-Part application, filed April 2, 1993; said application subsequently issued as U.S. Pat. No. 5,585,254). Further, Maxwell et al. discourage the use of recombinant retrovirus vectors for gene delivery, as they are "quite labile, grow to relatively low titers (particularly recombinant retroviruses), are difficult to handle without significant infectivity loss, and exhibit a limited host range." (see col. 1, lines 50-62). Thus, the disclosures prior to the April 2, 1993 application cannot constitute prior art against the instant claims since they fail to guide one of skill in the art toward the present invention. In addition, they teach away from the present invention which teaches that parvoviral constructs can be produced in high amounts and retain oncoselectivity against cancer cells.

Applicant respectfully submits that Maxwell et al. first disclose and teach the use of autonomous parvoviral vectors for delivering genes to target cells in their April 2, 1993 application, which is a Continuation-in-Part of abandoned application Serial No. 07/685,628, filed April 15, 1991. Applicant claims priority to the accompanying Belgian Application, filed December 10, 1992, prior to Maxwell et al. Applicant submits that the accompanying Belgian Application teaches the use of autonomous parvoviral vectors for delivering genes to target cells prior to Maxwell et al.'s teaching. Thus, Maxwell et al. cannot constitute prior art against the instant claims.

In view of the foregoing, Applicant respectfully requests withdrawal of the rejection to the claims under 35 U.S.C. § 102(e) and 103(a).

II. Sequence Submission Statement

A copy of the Sequence Listing in computer readable format as required by 37 C.F.R. § 1.821(e) is submitted herewith.

As required by 37 C.F.R. § 1.821(f), I hereby declare that the information recorded on the enclosed disk is identical to the printed Sequence Listing in the submitted herewith. As each of the sequences provided in the Sequence Listing was present in the specification as filed, no new matter has been added.

III. Conclusion

Applicants have provided herewith a printed version of the Sequence Listing and a copy of the Sequence Listing in computer readable format. The specification has been amended to conform to U.S. practices by incorporating a sequence identification number after each sequence listed in the specification on pages 47 and 50. In addition, Applicants have provided a certified English translation of the priority document, Belgian Application No. 09201087 (filed December 10, 1992).

The changes made to specification by the current amendment, including insertions and **[deletions]**, are shown on an attached sheet entitled **VERSION WITH MARKINGS TO SHOW CHANGES MADE**, which follows the signature page of this amendment. No new matter has been added herewith.

If any issues remain that may be addressed by a phone conversation, the Examiner is invited to contact the undersigned at the phone number listed below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: July 2, 2002

By: Daniel Hart

Daniel Hart
Registration No. 40,637
Attorney of Record
620 Newport Center Drive
Sixteenth Floor
Newport Beach, CA 92660
(619) 235-8550

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

On page 47, the paragraph beginning at line 18 has been amended as follows:

The fragment HindIII-SspI containing the 3'end region coding for the capsids of MVM in plasmid PMM984 is inserted in the corresponding sites of pUC19. The SspI site is transformed in a NsiI site by the addition of the linker NsiI (5'TGCATGCATGCA-3' SEQ ID NO: 1). The HindIII-NsiI fragment is inserted in the HindIII et NsiI site of the plasmid pPolyA (where the HindIII site was transformed into a NsiI site) according to the method of Spegelaere P., et al, (Journal of Virology 65: 4919, (1991)) in front of the SV40 polyadenylation signal.

On page 50, the paragraph beginning at line 25 has been amended as follows:

- The CMV promoter (38-682) including the Kozak consensus translation initiation site was amplified by PCR with the PWO Polymerase® (Boehringer) with the following primer:

5' CCATGGCATAGCCCATATATGGAGTTCCGCG 3' (SEQ ID NO: 2)

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